PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk Factors for Hospitalization and Death from COVID-19: A Prospective Cohort Study in South Sudan and Eastern Democratic Republic of the Congo
AUTHORS	Leidman, Eva; Doocy, Shannon; Heymsfield, Grace; Sebushishe, Abdou; Mbong, Eta Ngole; Majer, Jennifer; Bollemeijer, Iris

VERSION 1 – REVIEW

REVIEWER	Jones, S New York University School of Medicine
REVIEW RETURNED	18-Feb-2022

GENERAL COMMENTS	Overall This paper describes the characteristics of patients with COVID and their outcomes in South Sudan and DRC. Its strength is that it included all cases from selected health care systems and therefore represents the spectrum of a wide range of clinical severity. This paper is important as few studies have examined risk factors in resource scare context. My only concern is to what extent hospital supported by International Medical Corps are representative in the wider region. This paper is well written and easy to understand and should be accepted with very minor revisions. I gave a number of minor comments. Introduction: Page 4 - Line 13 error in reference Methods: Can the authors comment on to what extent are the 5 system operated by International Medical Corps representative of their host countries? Page 6 – line 10: I guess MUAC is mid upper arm circumference? Please expand on first usage. Page 6 – 28-35. GLMM logit link sems reasonable choice, but there are others possibilities. . But perhaps the authors could add a single sentence justifying choice? Page 6- line 46 I wish more papers included a patient and public involvement statement like this paper The Table 1&2 and 3&4 use slightly different conventions for number of decimal places for p values.

	Page 8 - Table 2 – Thanks for including N so we can work out missing values Table 3- line 34 – Presumably should read 1.83 (0.91-3.70) Line 54 – should read Anemic ^4

REVIEWER	Mills, Edward J McMaster University
REVIEW RETURNED	09-Mar-2022

GENERAL COMMENTS	This is a very well conducted study on an important topic. The authors should be commended for such a thorough study under the harsh conditions that would normally be the case in these settings, but made much harder due to COVID. For that reason, this article is quite exceptional. I have some comments below that the authors should consider. All should be considered minor. 1) The article is overly lengthy and could really benefit from trimming it down to the usual length of about 3000 words. All other aspects could be in an appendix. 2) Could you clarify the extent of lock-down occurring over time in those settings? 3) What were the treatments available for both out-patient and in-patient settings? For example, was dexamethasone or other steroids available and utilized? 4) I would simplify table 3. No point in putting both unadjusted and adjusted odds in there, just pick the adjusted. Also, I do not think that the symptoms individually add much. 5) Could you clarify the extent to which follow-up occurred? 6) At the point of enrolment, were all patients enrolled based on a covid positive test?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Prof. S Jones, New York University School of Medicine

Comments to the Author:
Overall

This paper describes the characteristics of patients with COVID and their outcomes in South Sudan and DRC. Its strength is that it included all cases from selected health care systems and therefore represents the spectrum of a wide range of clinical severity. This paper is important as few studies have examined risk factors in resource scare context. My only concern is to what extent hospital supported by International Medical Corps are representative in the wider region. This paper is well written and easy to understand and should be accepted with very minor revisions.

I gave a number of minor comments.

Introduction:
Page 4 - Line 13 error in reference

These should be a reference to articles 1 (CDC, 2021) and 2 (Zhou, 2020). Formatting has been corrected.

Methods:
Can the authors comment on to what extent are the 5 system operated by International Medical Corps representative of their host countries?

Characteristics of the study facilities are described in the Supplemental Table. Site operated or supported by IMC were purposively selected to ensure that IMC clinical staff could ensure adequate supervision and oversight of study enrollment. These sites however are likely better funded than health facilities on average in the country. The health facility in Juba, South Sudan was the only referral facility for COVID-19 in the country. Sites in DRC included public hospitals, an outpatient clinic, and an NGO operated health center and may better represent the diversity of care options in country.

We have added the following language to the limitation section of the manuscript to reflect the representativeness of our site:
"Finally, to ensure rigorous supervision the study sites were all operated or supported by IMC and may therefore be better resourced than other health facilities in the two countries."

Page 6 – line 10: I guess MUAC is mid upper arm circumference? Please expand on first usage.

Revised as suggested.

Page 6 – 28-35. GLMM logit link sems reasonable choice, but there are others possibilities. . But perhaps the authors could add a single sentence justifying choice?

Generalized linear mixed models (or GLMMs) are as an extension of generalized linear models (e.g., logistic regression) to include both fixed and random effects; in our models, facility of enrollment was included as a random effect. Inclusion of a random effect allowed us to account for potential clustering of our outcome by health facility given differences in access to medication, staffing, and quality of care – parameters we were unable to adjust for directly in the models. In other words, a GLMM allowed us to model a non-independent (or clustered) binary response (e.g., mortality and hospitalization) conditional on the attributes of each individual cluster (e.g., health facility) as a function of covariates.

We have revised the methods section such that this is more explicit:
"Two-level GLMMs were fitted using a logit link to account for the expected correlation in outcomes within health facilities which may be observed given differences in access to medication, staffing, or quality of care available at each facility."

Page 6- line 46 I wish more papers included a patient and public involvement statement like this paper

Thank you.

The Table 1&2 and 3&4 use slightly different conventions for number of decimal places for p values.

We have revised for consistency. In all tables we now have 2 decimals unless $p<0.01$ in which case we include 3 decimals.

Page 8 - Table 2 – Thanks for including N so we can work out missing values
Thank you.

Table 3- line 34 – Presumably should read 1.83 (0.91-3.70)
Yes, the 0 in 3.70 was inadvertently dropped. Revised as suggested.

Line 54 – should read Anemic ^4
Yes, the footnote should be superscript. Revised as suggested.

Reviewer: 2
Dr. Edward J Mills, McMaster University

Comments to the Author:
This is a very well conducted study on an important topic. The authors should be commended for such a thorough study under the harsh conditions that would normally be the case in these settings, but made much harder due to COVID. For that reason, this article is quite exceptional. I have some comments below that the authors should consider. All should be considered minor.

1) The article is overly lengthy and could really benefit from trimming it down to the usual length of about 3000 words. All other aspects could be in an appendix.

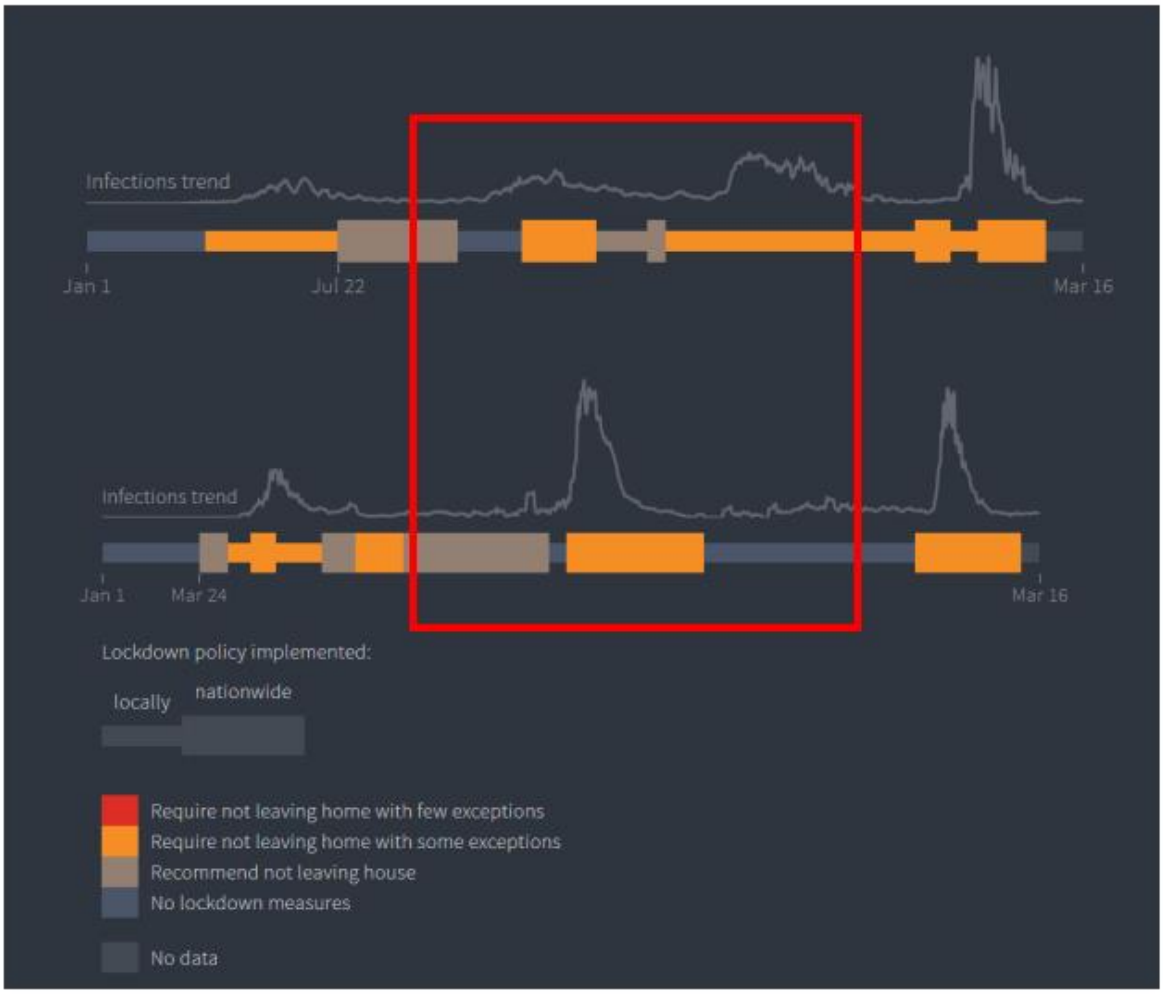
The manuscript is currently only 3,059 words. We have already trimmed the manuscript to ensure we are focusing on key findings and request the editors to allow for the manuscript as currently presented.

2) Could you clarify the extent of lock-down occurring over time in those settings?

The following graphs are produced by Reuters and illustrate the status of stay-at-home orders / lockdowns by country. The graph on top is DRC and on bottom is South Sudan. The red box is added to highlight the approximate dates of the study enrollment. As you can see, lockdown policies were variable throughout the study, transitioning from recommendations to requirements during periods of increased transmission.

Of note, policies and implementation varied by region. Our field teams note that in DRC, lockdowns of schools, churches, restaurants, and offices were in place in our study sites from March to July 2020. Schools were closed again from November 2020 to March 2021. Between July 2020 and February 2022, there was a curfew in place between 10pm and 4am.

Source: https://graphics.reuters.com/world-coronavirus-tracker-and-maps/countries-and-territories/democratic-republic-of-the-congo/ and https://graphics.reuters.com/world-coronavirus-tracker-and-maps/countries-and-territories/south-sudan/



3) What were the treatments available for both out-patient and in-patient settings? For example, was dexamethasone or other steroids available and utilized?

We have a companion manuscript under revision currently that focuses on in-patient care that includes detailed information on therapeutics available and received. We have added a reference to this manuscript to the methods. In short, oxygen concentrators and cylinders were available at all facilities (with varying supply availability); mechanical ventilators were only available at the Juba facility. In terms of therapeutics, steroids (including dexamethasone) and vasopressors were available at all facilities; antibodies and convalescent plasma were not available at any facilities.

For patients treated at home (outpatient), paracetamol and Vitamin C supplementation were available in both countries. Oral rehydration solution (ORS) was distributed on a case-by-case basis in South Sudan. Hydroxychloroquine and Azithromycin tablets were available as needed in DRC.

4) I would simplify table 3. No point in putting both unadjusted and adjusted odds in there, just pick the adjusted. Also, I do not think that the symptoms individually add much.

We think there is value in having both adjusted and unadjusted parameters such that readers can see that the risk factors are relatively insensitive to patient demographic and site characteristics. We have retained them for now but can revise if the editors prefer this information is removed.

Inclusion of the various symptoms is seen as highly valuable given ongoing work to evaluate which of the symptoms are used in algorithms for triaging patients to inpatient v. outpatient care, and determining severity at initial consult. For example, we highlight in the conclusions of our manuscript that respiratory symptom (shortness of breath as well as measured 02) are much more strongly associated with mortality than other symptoms, such that triage based on these symptoms likely better utilizes limited resources than screening for less sensitive symptoms such as fever.

5) Could you clarify the extent to which follow-up occurred?

Follow-up for inpatients was daily whereas follow-up for outpatients was weekly. This information has been added to the methods.

6) At the point of enrolment, were all patients enrolled based on a covid positive test?

This information is included in the methods:
“Cases with a positive real-time reverse transcription polymerase chain reaction (RT-PCR) or antigen test and inpatients not tested meeting the national suspect case definitions were eligible for enrollment. Cases were excluded from analysis if they tested negative following enrollment, were lost to follow-up (before recovery or death), or were transferred to another facility for care.”
We include the following additional information in Figure 1:
“Cases were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) (90% of confirmed cases) or antigen tests (10% of confirmed cases)”

VERSION 2 – REVIEW

REVIEWER	Mills, Edward J McMaster University
REVIEW RETURNED	06-Apr-2022

GENERAL COMMENTS	The authors have adequately addressed all of my comments.